

## TOPICAL REVIEW

# The neglected role of insulin-like growth factors in the maternal circulation regulating fetal growth

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Maternal insulin-like growth factors (IGFs) play a pivotal role in modulating fetal growth via their actions on both the mother and the placenta. Circulating IGFs influence maternal tissue growth and metabolism, thereby regulating nutrient availability for the growth of the conceptus. Maternal IGFs also regulate placental morphogenesis, substrate transport and hormone secretion, all of which influence fetal growth either via indirect effects on maternal substrate availability, or through direct effects on the placenta and its capacity to supply nutrients to the fetus. The extent to which IGFs influence the mother and/or placenta are dependent on the species and maternal factors, including age and nutrition. As altered fetal growth is associated with increased perinatal morbidity and mortality and a greater risk of developing degenerative diseases in adult life, understanding the role of maternal IGFs during pregnancy is essential in order to identify mechanisms underlying altered fetal growth and offspring programming.

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**Abbreviations** AIB, amino isobutyric acid; CR, crown–rump; D, day of pregnancy; GH, growth hormone; hCG, human chorionic gonadotropin; hPL, human placental lactogen; IGF, insulin-like growth factor; IGFBP, IGF binding protein; P, postnatal day; PL, placental lactogen.

## Introduction

The insulin-like growth factors (IGFs) IGF-I and IGF-II are 7.5 kDa single-chained polypeptides that promote growth both before and after birth. They affect the metabolism, mitogenesis and differentiation of a wide variety of cell types, including those of the placenta by binding to IGF receptors (IGF1R and IGF2R), insulin receptor (InsR) and a hybrid IGF1R–InsR receptor. Their bioavailability is influenced by at least six IGF binding proteins (IGFBP-1 to IGFBP-6) that prolong the IGF half-life in the circulation and transport IGFs to their receptors. Together, the IGFs, their receptors and binding proteins form the IGF axis, which is responsive to a range of environmental signals including nutrients, oxygen and hormones, such as growth hormone (GH), cortisol, insulin, thyroid hormones and sex steroids.

Before birth, IGFs are paracrine growth regulators synthesised by multiple fetal tissues, independently of GH. Although IGF-II is the most abundant fetal IGF, deletion of either *Igf* gene in mice reduces birth weight to 60% of wildtype (Louvi *et al.* 1997; Fowden, 2003).

Effects of IGFs on fetal growth are additive, as deletion of *Igf1r*, through which both IGFs act, reduces birth weight to a greater extent than deletion of either *Igf1* or *Igf2* alone (Louvi *et al.* 1997). Whilst IGF-I appears to regulate fetal growth in response to nutrient availability,

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IGF-II is thought to provide the constitutive stimulus for fetoplacental growth (Fowden, 2003). Circulating IGF-I concentrations rise after birth due primarily to the onset of GH-dependent hepatic synthesis of IGF-I although a variety of other tissues also continue to produce IGF-I. This endocrine IGF-I production drives growth postnatally. In contrast, IGF-II expression declines towards term in association with pre-partum maturation of specific tissues, although IGF-II still circulates in plasma of several species postnatally (Gargosky *et al.* 1990; Giudice *et al.* 1993; Sohlstrom *et al.* 1998; Perry *et al.* 2002). However, in adult mice, IGF-II is confined to the brain and is not detectable in plasma (Fielder *et al.* 1990). After postnatal growth is complete, the role of IGFs is less clear. They are thought to be involved in the turnover and growth of adult tissues during physiological conditions, such as wound healing, exercise and pregnancy. This review examines the maternal IGF system during pregnancy and its effects on fetal growth, with particular emphasis on the actions of IGFs on maternal metabolism and nutrient partitioning and on placental growth and function. Since the pattern of fetal growth determines rates of morbidity and mortality at, and long after, birth (Barker, 2004), understanding the role of maternal IGFs during pregnancy may help identify the mechanisms involved in developmental programming of life expectancy.

### Maternal IGF concentrations

Maternal plasma IGFs during pregnancy depend on species and gestational age (Fig. 1). In species like humans, rabbits and guinea pigs, maternal IGF-I concentrations increase in the first half of pregnancy (Fig. 1: Gargosky *et al.* 1990; Nason *et al.* 1996; Sohlstrom *et al.* 1998). In women, IGF-I levels continue to rise throughout pregnancy, whilst in rabbits and guinea pigs, the elevated IGF-I levels decline rapidly from mid-pregnancy onwards (Fig. 1). In the baboon, rhesus monkey, rat and pig, maternal circulating IGF-I concentrations fall during pregnancy to as low as 30% of non-pregnant values (Giudice *et al.* 1993; Farmer *et al.* 2000; Van Mieghem *et al.* 2009). In some species like cattle and sheep, plasma IGF-I is unaltered by pregnancy (Fig. 1: Wallace *et al.* 1997; Perry *et al.* 2002; Weber *et al.* 2007; de Boo *et al.* 2008). In mice dams, plasma IGF-I at mid-pregnancy is ~70% lower than in virgin and early pregnant females but nothing is known about concentrations in late pregnancy (Travers *et al.* 1990).

The IGF-II profile in maternal plasma is more consistent across species than for IGF-I, with an overall rise in concentrations during pregnancy (Fig. 1). In some animals, the increase is marginal, whereas in others like rabbits, there is a 200-fold increment by

mid-gestation (Fig. 1: Nason *et al.* 1996). In rat dams, plasma IGF-II increases with advancing gestation, whereas in women, levels are maintained after the initial elevation, throughout pregnancy (Fig. 1: Gargosky *et al.* 1990; Van Mieghem *et al.* 2009). In non-human primates and rabbits, maternal plasma IGF-II declines towards term but remains higher than non-pregnant values (Fig. 1). In cows and guinea pigs, plasma IGF-II concentrations are relatively unresponsive to pregnancy (Sohlstrom *et al.* 1998; Perry *et al.* 2002). Irrespective of reproductive state, IGF-II is more abundant than IGF-I in most species studied (Gargosky *et al.* 1990; Giudice *et al.* 1993; Nason *et al.* 1996; Sohlstrom *et al.* 1998).

### Sources of maternal IGFs

There are several potential sources of IGFs during pregnancy. In several species, IGFs are produced by a range of tissues that may increase in mass during pregnancy including the liver, uterus, skeletal muscle and adipose tissue (Peter *et al.* 1993; Coleman *et al.* 1994; Sterle *et al.* 1998; Olausson & Sohlstrom, 2003). Indeed, in women, the increased maternal IGF-I concentration in early-mid pregnancy is thought to reflect growth of maternal tissues (Lof *et al.* 2005). In rabbits, maternal whole body tissue growth and subsequent tissue mobilisation are associated with elevated and then reduced IGFs in early and late gestation, respectively (Nason *et al.* 1996). As adipose tissue accounts for a greater proportion of maternal body mass during pregnancy, it may contribute significantly to the circulating pool of IGFs. However, as blood volume rises in parallel with maternal body mass, increased tissue mass is unlikely to be the sole explanation for the rise in maternal IGFs during pregnancy.

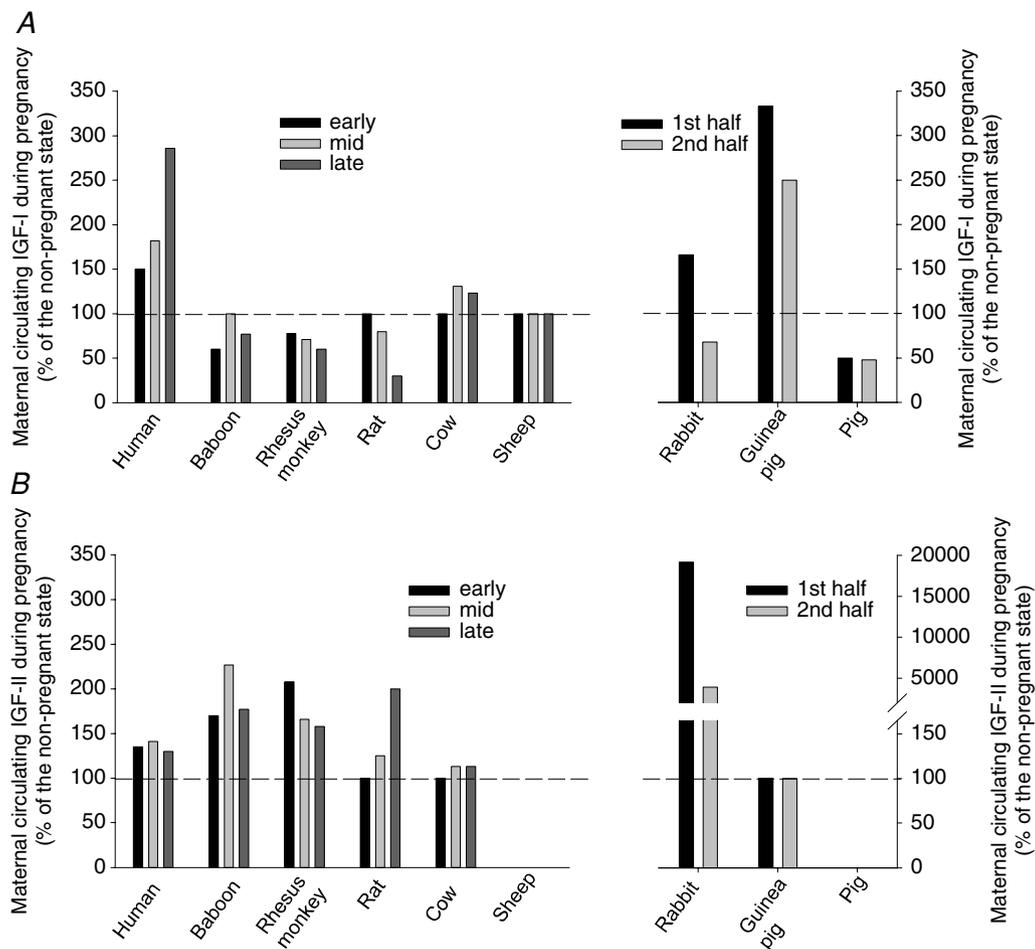
Studies performed mainly in the guinea pig have shown that *Igf* expression is increased in some, but not all, tissues per unit mass during pregnancy (Sohlstrom *et al.* 1998; Olausson & Sohlstrom, 2003). For instance, there is no increase in *Igf* mRNA expression by maternal muscle, although its mass is increased. In contrast, *Igf* mRNA abundance in maternal liver and fat increase early in pregnancy and are maintained until term, especially for *Igf1*, despite reductions in hepatic and adipose tissue weight during the second half of pregnancy. Furthermore, uterine expression of *Igf1* mRNA is reduced during guinea pig pregnancy. Thus, in early pregnancy, an increase in *Igf* expression by the liver and adipose tissue plus expansion of muscle mass in the mother, may contribute to her elevated plasma IGF-I. In late pregnancy, the reduced liver and fat mass combined with down-regulated uterine *Igf1* gene expression may explain the pre-partum decline in plasma IGF-I levels (Sohlstrom *et al.* 1998; Olausson & Sohlstrom, 2003). In rats, the fall in maternal IGF-I concentration, particularly in the

second half of pregnancy, coincides with reduced hepatic *Igf1* gene expression (Donovan *et al.* 1991). In part, the changes in tissue growth and *Igf* gene expression during pregnancy may relate to the altered maternal endocrine environment. Indeed, somatotropin and steroid hormone concentrations alter during pregnancy and are known to regulate IGF production (Handwerger & Freemark, 2000; Mullis & Tonella, 2008); however, definitive studies are required.

Another potential source of maternal IGFs is the placenta. In all species studied, the placenta synthesises IGF-II, at least in early pregnancy. In haemochorial placentas of humans, guinea pigs, rhesus monkeys, baboons, rats and mice, IGF-II is produced by the syncytiotrophoblast layer in direct contact with maternal blood (Han & Carter, 2000; Nayak & Giudice, 2003; Sferruzzi-Perri *et al.* 2006). In rodents, the placenta is likely to be a major IGF-II source as *Igf2* gene expression is

limited in adult peripheral tissues. In humans, IGF-II is also produced abundantly by the extravillous trophoblasts lining the uterine spiral arteries (Han & Carter, 2000). In contrast to IGF-II, the placenta is an unlikely source of IGF-I as it expresses very little (Han & Carter, 2000). However, the placenta may influence maternal plasma IGF-I indirectly through secreting hormones which modulate IGF-I synthesis in maternal tissues. For instance, human syncytiotrophoblast secretes a variant of growth hormone, placental growth hormone (PGH), which stimulates maternal IGF-I production despite a fall in pituitary GH secretion (Alsat *et al.* 1998). Similarly, the placenta secretes placental lactogen (PL) into the maternal circulation, which is thought to modulate maternal IGF-I expression, although direct evidence for this is limited (Handwerger & Freemark, 2000; Karabulut *et al.* 2001).

Changes in maternal circulating IGFs during pregnancy may also be due to post-translational processes. In



**Figure 1. The changes in maternal circulating concentrations of IGF-I (A) and IGF-II (B) during pregnancy expressed as a percentage of the non-pregnant state (represented as the dashed line) with respect to the stage of pregnancy**

The data presented are from the following references: Gargosky *et al.* 1990; Giudice *et al.* 1993; Nason *et al.* 1996; Wallace *et al.* 1997; Sohlstrom *et al.* 1998; Farmer *et al.* 2000; Perry *et al.* 2002; Weber *et al.* 2007; de Boo *et al.* 2008; Van Mieghem *et al.* 2009.

pregnant women and rats, IGF-II secreted as a biologically inactive pro-peptide undergoes proteolytic cleavage to become active (Qiu *et al.* 2005, 2007; Van Mieghem *et al.* 2009). Proteolytic activation increases during pregnancy and correlates with maternal circulating IGF-II concentrations (Qiu *et al.* 2005, 2007; Van Mieghem *et al.* 2009). In addition, the expression, covalent modifications and circulating levels of IGFBPs change in the mother during pregnancy and may influence circulating IGF profiles and bioavailability, as reviewed previously (Fielder *et al.* 1990; Donovan *et al.* 1991; Giudice *et al.* 1993; Nason *et al.* 1996; Sohlstrom *et al.* 1998; Forbes & Westwood, 2008).

### The roles of maternal IGFs in fetal growth regulation

Maternal plasma IGFs correlate positively with fetal growth and birth weight in several species. In mice, cross-breeding experiments between lines selected for high or low plasma IGF-I levels reveal that elevated maternal circulating IGF-I abolishes the normally negative relationship between fetal mass and litter size in late gestation (Gluckman *et al.* 1992). Experimental manipulations of maternal IGFs by exogenous IGF treatment or elevated endogenous IGF production (via GH infusion) impacts on fetal growth (Table 1). Fetal actions of the IGFs depend on species, the specific treatment regime (length and timing during pregnancy), litter size, maternal age, parity, nutritional state and the time in pregnancy when outcomes were assessed (during or after treatment). Since IGFs and GH do not cross the placenta in significant quantities (Davenport *et al.* 1990), the effects of the IGFs on fetal growth must occur indirectly through actions on maternal metabolism and nutrient partitioning, and/or placental development and function.

### Maternal metabolism and nutrient partitioning

In rat dams, positive nitrogen balance during early pregnancy is correlated with circulating IGF concentrations (Palmer *et al.* 1996; Nakago *et al.* 1999). Elevating maternal IGF-I by IGF-I or GH administration in the second half of rat pregnancy stimulated growth of maternal tissue without an affect on fetal growth (Table 1: Gargosky *et al.* 1991; Woodall *et al.* 1999). In addition, reducing maternal IGF-I in the second half of pregnancy using antibodies against GH, repartitioned maternal muscle protein to growth of the rat pup (Palmer *et al.* 1996). This suggests that, in rats, declining maternal IGF-I concentrations in late pregnancy may limit maternal anabolic activity to divert substrates to the gravid uterus. A similar decline in maternal IGF-I occurs in guinea pigs during late pregnancy although levels remain higher than pre-pregnancy (Sohlstrom *et al.* 1998). Elevating maternal plasma IGF-I in early

guinea pig pregnancy increases uptake of amino acid and glucose by maternal visceral organs, reduces maternal adiposity and increases fetal growth, near term long after cessation of treatment (Sohlstrom *et al.* 2001; Sferruzzi-Perri *et al.* 2006, 2007*a,b*). Overall, these studies indicate that maternal IGF-I is important in resource allocation between maternal tissues and the growing conceptus but that its endocrine actions are dependent on species and gestational age.

In pigs, in which plasma IGF-I is lower in pregnant than non-pregnant states, elevating endogenous IGF-I during the first half of pregnancy by maternal GH administration increased growth of maternal tissues (Table 1: Kelley *et al.* 1995; Sterle *et al.* 1995; Okere *et al.* 1997; Rehfeldt *et al.* 2001; Schneider *et al.* 2002; Gatford *et al.* 2009). In some of these studies, elevating plasma IGF-I in pig mothers was also associated with increased plasma concentrations of glucose, insulin and free fatty acids and enhanced fetal growth and/or survival (Table 1). These studies suggest that maternal IGF-I may drive fetal growth by promoting maternal insulin resistance and thus increasing substrate availability for the gravid uterus. Certainly, maternal IGF-I appears to have the most beneficial effects on fetal development when maternal nutrient supply is limited. For instance, elevating maternal IGF-I endogenously enhances maternal back fat loss during pregnancy and increases fetal growth in undernourished pigs (Gatford *et al.* 2000).

In sheep, elevating plasma IGF-I by maternal GH treatment in early pregnancy increases maternal nutrient concentrations and sometimes increases fetal weight at the expense of maternal tissue mass (Table 1: Stelwagen *et al.* 1994; Jenkinson *et al.* 1999; Wallace *et al.* 2004; Costine *et al.* 2005; Koch *et al.* 2010). However, in later pregnancy, increasing maternal circulating IGF-I appears to have no immediate effect on maternal body composition or fetal weight (Harding *et al.* 1997). The extent of IGF-I actions on the mother is dependent on gestational age, maternal age and nutrition, and whether the pregnancy is a singleton or twin (Table 1: Costine *et al.* 2005; Wallace *et al.* 2006*a*; Kenyon *et al.* 2007; Wright *et al.* 2008; Koch *et al.* 2010). Like the pig, maternal IGF-I may have most benefit on ovine fetal growth in adverse maternal environments. For instance, in the over-nourished adolescent ewe when there is increased competition for substrates by still-growing maternal tissues, GH treatment and elevated IGF-I between days 95 to 125 of pregnancy, reduces maternal adiposity and increases fetal growth (Wallace *et al.* 2006*b*). Furthermore, increasing maternal plasma IGF-I endogenously in late ovine pregnancy, shifts maternal metabolism in favour of the conceptus by increasing maternal plasma insulin, glucose and free fatty acids. This partially prevents the fetal growth restriction caused by placental embolization (de Boo *et al.* 2008).

**Table 1. The impact of elevated maternal plasma IGF-I, IGF-II or GH treatment on the mother and offspring**

Maternal treatment	Species	Gestational age (days) at		Outcomes for		References
		Treatment	Study (% of term)	Mother	Offspring	
IGF-I	Mouse	D1–19	D19 (95%)	↓ maternal constraint	↔ fetal weight litter size and fetal weight were no longer negatively associated	(Gluckman <i>et al.</i> 1992)
	Rat	D10–21	D21 (95%)	↑ weight gain during pregnancy	↔ fetal weight or viability	(Gargosky <i>et al.</i> 1991; Woodall <i>et al.</i> 1999)
	Guinea pig	D20–37	D40 (57%)	↔ weight gain, food efficiency, body composition ↔ circulating metabolites	↓ litter size by 27% ↑ fetal weight by 6%	(Sohlstrom <i>et al.</i> 2001)
		D20–38	D35 (50%) and D62 (90%)	On D35 and D63: ↑ tissue glucose and AIB uptake On D62: ↓ 30–50% adiposity	On D35 and D62: ↑ fetal weight by 15–17% On D62: ↑ fetal viability ↑ plasma a-amino nitrogen ↓ circulating cholesterol	(Sferruzzi-Perri <i>et al.</i> 2006, 2007a,b)
IGF-II	Rat	D16–22	D22 (100%)	↑ plasma volume expansion ↔ body weight	↔ fetal weight	(Van Mieghem <i>et al.</i> 2009)
	Guinea pig	D20–37	D40 (57%)	↔ weight gain, food efficiency ↔ circulating metabolites ↑ interscapular fat mass	↑ fetal weight by 7%	(Sohlstrom <i>et al.</i> 2001)
		D20–38	D35 (50%) and D62 (90%)	On D62: ↔ weight or body composition ↑ tissue AIB uptake ↔ circulating metabolites	On D62: ↑ fetal viability ↑ fetal weight by 11% ↑ circulating a-amino nitrogen	(Sferruzzi-Perri <i>et al.</i> 2006, 2007a,b)
Leu <sup>27</sup> IGF-II	Guinea pig	D20–38	D62 (90%)	↔ weight gain ↓ adiposity by 10–30% ↔ tissue uptake of glucose or AIB ↔ circulating metabolites	↔ fetal viability ↑ fetal weight by 11% ↑ circulating a-amino nitrogen ↓ circulating cholesterol ↓ circulating fatty acids	(Sferruzzi-Perri <i>et al.</i> 2008)
GH	Rat	D10–20	D20 (90%)	↑ weight gain	↔ fetal weight or body composition ↔ postnatal growth	(Woodall <i>et al.</i> 1999)

Table 1 Continued

Maternal treatment	Species	Gestational age (days) at		Outcomes for		References
		Treatment	Study (% of term)	Mother	Offspring	
GH	Pig	D10–27	D28 (25%)	↔ body weight ↑ lean body mass ↑ circulating insulin, glucose and free fatty acids	↑ fetal weight of runts	(Rehfeldt <i>et al.</i> 2001; Schneider <i>et al.</i> 2002)
		D25–50	D50 (45%)	↑ weight gain in sows ↔ weight gain in gilts In both sows and gilts: ↓ circulating urea	In both sows and gilts: ↑ fetal weight by 11%	(Gatford <i>et al.</i> 2009)
		D28–40	D41 (35%), P1 (100%)	↑ weight on D41 but ↓ by D105	↑ embryonic survival ↔ fetal weight ↑ fetal and postnatal CR length	(Kelley <i>et al.</i> 1995; Sterle <i>et al.</i> 1995)
		D30–70	D113 (100%)	ND	↔ fetal weight ↔ fetal viability	(Okere <i>et al.</i> 1997)
		D97–115	D113 (100%)	↑ circulating glucose ↑ circulating insulin ↑ circulating fatty acids	↔ birth weight	(Kveragas <i>et al.</i> 1986)
	Sheep	D7–30 Singleton and twin pregnancies	P1 (100%)	ND	In singleton but not twin pregnancies: ↑ birth weights by 10%	(Costine <i>et al.</i> 2005; Koch <i>et al.</i> 2010)
		D35–55 Only twin pregnancies	D55 (37%)	↔ weight gain	↔ fetal weight	(Wright <i>et al.</i> 2008)
		D70–84 or D98–112 Singleton and twin pregnancies	D85 (56%) or D113 (75%)	↔ energy intake ↑ uterine weight ↑ circulating insulin ↑ circulating fatty acids ↑ circulating glucose	D70–84: ↔ fetal weight D98–112: ↑ fetal weight by 9–11% (similar impacts on singles and twins)	(Jenkinson <i>et al.</i> 1999)
		D35–80	D81 (54%)	↔ food intake ↔ weight gain ↓ adiposity by ~20% ↑ liver mass ↑ circulating insulin, glucose and fatty acids ↓ circulating leptin	↔ fetal weight	(Wallace <i>et al.</i> 2004)

**Table 1 Continued**

Maternal treatment	Species	Gestational age (days) at		Outcomes for		References
		Treatment	Study (% of term)	Mother	Offspring	
GH	Sheep	D97–124	D125 (83%), P1 (100%)	↔ weight gain ↓ proportion of body fat	↔ fetal weight	(Stelwagen <i>et al.</i> 1994)
		D125–134	D134 (90%)	↔ energy intake ↔ body weight ↓ circulating urea ↑ circulating insulin	↔ fetal weight	(Harding <i>et al.</i> 1997)

AIB, amino isobutyric acid; CR, crown–rump; D, day of pregnancy; ND, not determined; P, postnatal day. For studies in sheep, pregnancies were singleton or otherwise stated. Average gestational length in days in: mice, 20; rats, 22; guinea pigs, 70; pigs, 112 and sheep, 150.

Compared to IGF-I, there is less information about the role of endocrine IGF-II in maternal metabolism and substrate partitioning (Table 1). In guinea pigs, elevating maternal IGF-II in early to mid pregnancy did not affect maternal body composition, whilst uptake of amino acids by maternal visceral organs was increased and fetal growth enhanced near term (Sferruzzi-Perri *et al.* 2006, 2007*a,b*). In contrast to native IGF-II, treatment of guinea pig dams with a synthetic analogue of IGF-II that selectively binds to IGF2R (Leu<sup>27</sup>-IGF-II), reduced maternal adiposity in late pregnancy without effects on substrate uptake by maternal tissues (Sferruzzi-Perri *et al.* 2008). The effects of Leu<sup>27</sup>-IGF-II on maternal body composition were similar to those of IGF-I, suggesting that some IGF-I-specific effects may be due to displacement of endogenous IGF-II from the IGF2R and its subsequent interaction with IGF1R and the InsR. In rats, IGF-II treatment in mid to late pregnancy increased maternal blood volume expansion without impacting on fetal growth (Table 1; Van Mieghem *et al.* 2009). Thus, maternal endocrine IGF-II may influence fetal growth by regulating maternal metabolic and cardiovascular adaptations to pregnancy; however, further studies are warranted.

### Placental development and function

Maternal endocrine IGFs may also affect fetal growth via placental actions. In addition to transporting nutrients, the placenta may modulate fetal development by secreting hormones, either into the umbilical circulation to directly affect fetal metabolism and growth, or into the maternal circulation to alter maternal metabolism and substrate availability for placental transfer. The placenta expresses IGF1R, IGF2R and InsR in several species and IGF1R-InsR hybrid in the human placenta (Zhou & Bondy, 1992; Soos *et al.* 1993; Fang *et al.* 1997; Hiden *et al.* 2006; Sferruzzi-Perri *et al.* 2006; Pringle & Roberts, 2007). More specifically, in women and guinea pigs, the IGF and insulin

receptors are localised to the syncytiotrophoblast layer bathed in maternal blood (Fang *et al.* 1997; Hiden *et al.* 2006; Sferruzzi-Perri *et al.* 2006). This permits endocrine regulation of placental growth and function by maternal IGFs (Table 2).

IGF-I and IGF-II prevent apoptosis and enhance proliferation and migration in human placental villous explants, primary trophoblast cultures or trophoblast cell lines from early pregnancy and term (Table 2; Irving & Lala, 1995; Hamilton *et al.* 1998; McKinnon *et al.* 2001; Lacey *et al.* 2002; Smith *et al.* 2002; Hills *et al.* 2004; Kabir-Salmani *et al.* 2004; Qiu *et al.* 2005; Forbes *et al.* 2008). Similarly, IGF-I stimulates proliferation and migration, whilst IGF-II promotes differentiation of murine ectoplacental cone trophoblast in culture (Kanai-Azuma *et al.* 1993). Furthermore, IGF-II promotes migration of ovine trophoblast cells *in vitro* (Kim *et al.* 2008).

In guinea pigs, maternal plasma IGF-I and IGF-II correlate positively with placental surface area for exchange and negatively with barrier thickness (Roberts *et al.* 2008). Treatment of guinea pig dams with either IGF in early to mid pregnancy increases fetal weight near term (Sferruzzi-Perri *et al.* 2006). Whilst there was no sustained effect of either IGF on placental weight, IGF-II increased the volume and surface area of the exchange region in late gestation (Table 2; Sferruzzi-Perri *et al.* 2006). Development of the placental exchange region was further enhanced when the IGF2R-selective synthetic analogue, Leu<sup>27</sup>-IGF-II was administered maternally (Sferruzzi-Perri *et al.* 2008). This suggests that maternal IGF-II in early gestation may act, in part, via the IGF2R to enhance functional development of the placenta.

In addition to stimulating placental growth, maternal endocrine IGFs may influence fetal growth by altering activity of the placental nutrient transporters. Both IGF-I and IGF-II stimulate glucose and amino acid uptake in human trophoblast *in vitro* (Kniss *et al.* 1994; Karl, 1995;

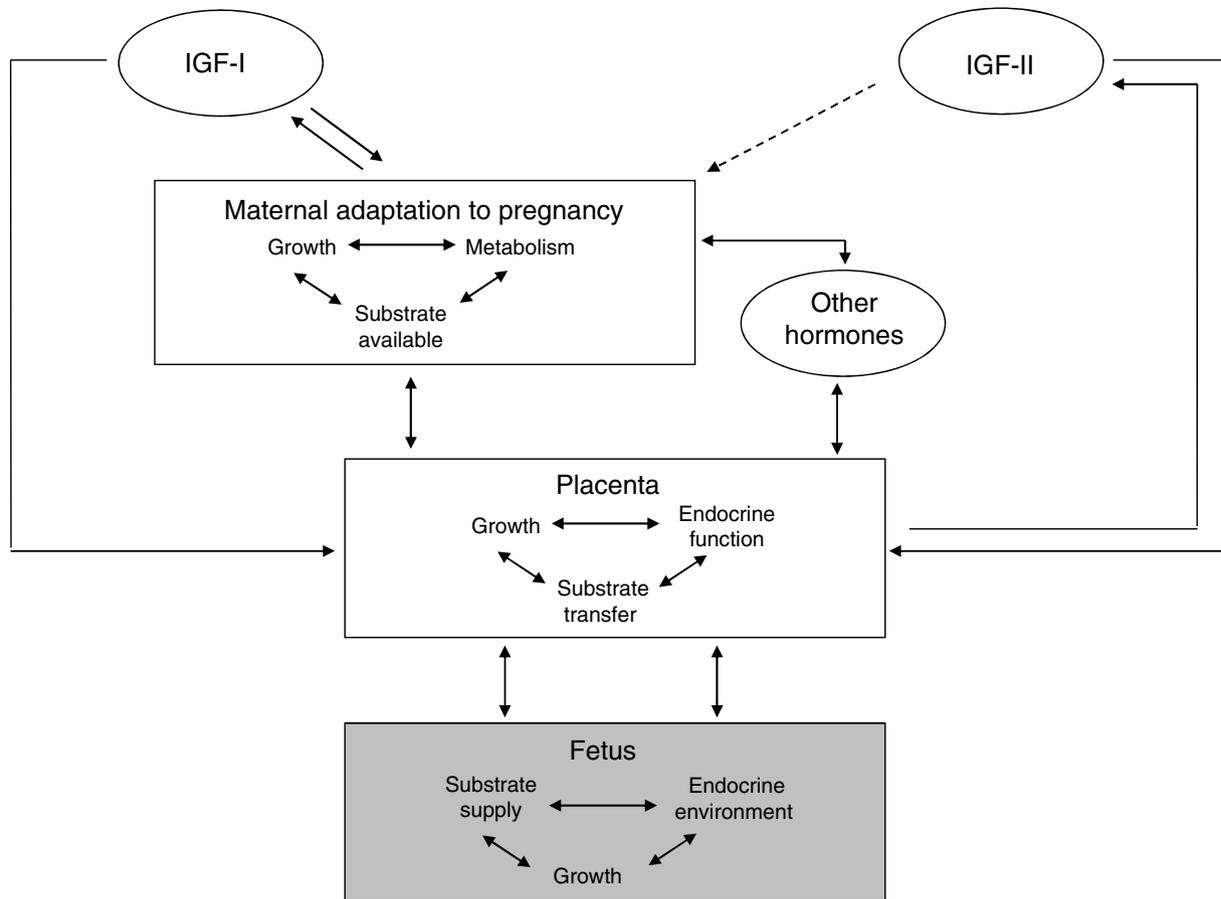
**Table 2. The impact of IGFs on placental growth and function *in vitro* and *in vivo***

Treatment	Species	Treatment (txt)	Analysis day	Placental outcome	References
IGF-I	Mouse	<i>In vivo</i> : maternal txt D1–19	D19	↔ weight	(Gluckman <i>et al.</i> 1992)
		<i>In vitro</i> : primary ectoplacental cone trophoblast	1st trimester	↑ proliferation ↑ migration	(Kanai-Azuma <i>et al.</i> 1993)
	Rat	<i>In vivo</i> : maternal txt D10–21	D21	↔ weight	(Gargosky <i>et al.</i> 1991; Woodall <i>et al.</i> 1999)
	Guinea pig	<i>In vivo</i> : maternal txt D20–37	D40	↑ weight by 10%	(Sohlstrom <i>et al.</i> 2001)
		<i>In vivo</i> : maternal txt D20–38	D35 and D62	↔ weight or structure ↑ transfer of glucose and AIB	(Sferruzzi-Perri <i>et al.</i> 2006, 2007a,b)
	Sheep	<i>In vivo</i> : maternal txt for 4 h on ~D132	D132	↑ lactate production	(Liu <i>et al.</i> 1994)
	Human	<i>In vitro</i> : villous explants	1st trimester	↑ trophoblast proliferation ↑ extravillous trophoblast migration ↓ trophoblast apoptosis	(Maruo <i>et al.</i> 1995; Lacey <i>et al.</i> 2002; Forbes <i>et al.</i> 2008)
			1st trimester	↑ secretion of hCG and hPL	(Maruo <i>et al.</i> 1995),
		<i>In vitro</i> : primary trophoblast	1st trimester	↑ proliferation ↑ migration ↑ invasion	(Hamilton <i>et al.</i> 1998; Hills <i>et al.</i> 2004; Kabir-Salmani <i>et al.</i> 2004)
			1st trimester and term	↑ glucose and amino acid uptake	(Kniss <i>et al.</i> 1994; Karl, 1995; Roos <i>et al.</i> 2009)
		<i>In vitro</i> : villous explants	Term	↓ release of vasoconstrictors	(Siler-Khodr <i>et al.</i> 1995)
		<i>In vitro</i> : primary villous and syncytialised trophoblast	Term	↓ TNF $\alpha$ - and IFN $\gamma$ -induced apoptosis	(Smith <i>et al.</i> 2002)
IGF-II	Mouse	<i>In vitro</i> : primary ectoplacental cone trophoblast	1st trimester	↑ differentiation into giant cells	(Kanai-Azuma <i>et al.</i> 1993)
			Rat	<i>In vivo</i> : maternal txt D16–22	D22
	Sheep	<i>In vitro</i> : primary mononuclear trophoblast	1st trimester	↑ migration	(Kim <i>et al.</i> 2008)
	Guinea pig	<i>In vivo</i> : maternal txt D20–37	D40	↑ weight by 9%	(Sohlstrom <i>et al.</i> 2001)
		<i>In vivo</i> : maternal txt D20–38	D35 and D62	↔ weight ↓ area and proportion of the interlobium ↑ labyrinthine area, proportion and volume ↑ surface area for exchange ↔ thickness of the trophoblast barrier for exchange ↑ transfer of glucose	(Sferruzzi-Perri <i>et al.</i> 2006, 2007a,b)

**Table 2 Continued**

Treatment	Species	Treatment (txt)	Analysis day	Placental outcome	References
IGF-II	Human	<i>In vitro</i> : villous explants	1st trimester	↑ trophoblast proliferation ↑ syncytial regeneration ↑ extravillous trophoblast cell migration ↓ trophoblast apoptosis	(Lacey <i>et al.</i> 2002; Forbes <i>et al.</i> 2008)
		<i>In vitro</i> : primary trophoblast	1st trimester	↑ proliferation ↑ migration ↑ invasion	(Irving & Lala, 1995; Hamilton <i>et al.</i> 1998; McKinnon <i>et al.</i> 2001; Hills <i>et al.</i> 2004; Qiu <i>et al.</i> 2005)
		<i>In vitro</i> : primary villous trophoblast	1st trimester and term	↑ glucose and amino acid uptake	(Kniss <i>et al.</i> 1994; Karl, 1995)

AIB, amino isobutyric acid; D, day of pregnancy; hCG, human chorionic gonadotropin; hPL, human placental lactogen; txt, treatment.



**Figure 2. The proposed actions of maternal circulating IGFs on the mother and placenta that drive fetal growth**

Circulating IGFs influence maternal tissue growth and metabolism and thereby modulate nutrient availability for conceptus growth. Maternal IGFs also regulate placental morphogenesis, substrate transport and hormone secretion, which influence fetal growth by indirect effects on maternal substrate availability, or by direct impacts on placental capacity to supply nutrients to the fetus and the fetal endocrine environment. These actions of plasma IGFs on the mother and placenta influence fetal growth, metabolism and endocrine state, which in turn, may signal back to the placenta to alter its phenotype.

Roos *et al.* 2009). In the late pregnant ewe, acute maternal IGF-I treatment alters placental metabolic function, which suggests enhanced glucose and lactate delivery to the fetus (Liu *et al.* 1994). In guinea pigs, elevated maternal plasma IGF-I or IGF-II during early to mid pregnancy increases placental capacity to deliver glucose and/or amino acids to the fetus in late gestation (Table 2: Sferruzzi-Perri *et al.* 2006, 2007*a,b*). Placental substrate transfer was increased in late gestation, partly due to enhanced expression of nutrient transporters by IGF-I in mid pregnancy and improved development of the exchange region by IGF-II in late pregnancy (Sferruzzi-Perri *et al.* 2006, 2007*b*). In culture, IGF-I prevents the release of the vaso-constrictors prostaglandin E and F, and thromboxane, by the term human placenta (Table 2: Siler-Khodr *et al.* 1995). *In vivo*, these effects could influence utero-placental blood flow and substrate transfer in late gestation. Indeed, reduced maternal circulating IGF-I or increased maternal circulating inactive pro-IGF-II in women, are associated with abnormal placental blood flows and small for gestational age and growth-restricted babies (Holmes *et al.* 1997; Qiu *et al.* 2005).

IGFs enhance placental secretion of hormones including progesterone, human chorionic gonadotrophin and PL *in vitro* (Maruo *et al.* 1995). In addition, IGF-II simulates the differentiation of hormone-producing cells in murine and ovine trophoblast *in vitro* and the development of the endocrine trophospongial zone of the rat placenta, *in vivo* (Kanai-Azuma *et al.* 1993; Kim *et al.* 2008; Van Mieghem *et al.* 2009). IGF-induced changes in placental hormone production may influence fetal growth directly or indirectly. For instance, PL secreted into the umbilical circulation promotes secretion of growth promoting hormones, such as insulin and IGF-I and IGF-II in the fetus, whilst in the mother, PL and progesterone induce maternal insulin resistance, favouring glucose delivery to the fetus for growth (Butte, 2000; Handwerger & Freemark, 2000; Karabulut *et al.* 2001). Thus, maternal endocrine IGFs may influence fetal growth by altering placental development, hormone secretion and substrate transport.

### Conclusions and perspectives

IGFs in the maternal circulation are emerging as important regulators of fetal growth via their actions on both the mother and the placenta (Fig. 2). They influence maternal tissue growth and metabolism and, thereby, modulate nutrient availability for conceptus growth. They also regulate placental morphogenesis, substrate transport and hormone secretion, which influence fetal growth either via indirect effects on maternal substrate availability, or through direct impacts on fetal nutrient supply and its endocrine environment (Fig. 2). In turn, changes in fetal

growth, metabolism and endocrine state induced by the actions of maternal plasma IGFs may signal back to the placenta to alter its phenotype further (Harding *et al.* 1994; Constancia *et al.* 2005). Overall, maternal IGF-I and IGF-II may have complementary but overlapping roles in optimising fetal nutrient acquisition for growth and survival. Maternal IGF-I appears to act predominantly on maternal tissues to influence substrate availability, whereas maternal IGF-II acts on the placenta to influence substrate delivery to the fetus (Fig. 2). The relative balance of IGF actions on the mother and placenta in regulating fetal growth depends not only on the abundance of the two IGFs, but also on the species, stage of pregnancy, and age and nutritional state of the mother. Maternal IGF administration may, therefore, have benefits to the food and livestock industry by providing a means of improving animal productivity; however, further studies are warranted. Furthermore, in animal models of intra-uterine growth, elevating maternal IGF concentrations appears to improve fetal growth, suggesting the possibility for clinical translation (Gatford *et al.* 2000; Wallace *et al.* 2006*b*; de Boo *et al.* 2008). Before this approach could be used therapeutically to improve fetal growth in compromised human pregnancies, further studies are required to identify the potential long-term effects on both the mother and her offspring with respect to tissue growth and endocrine function. Furthermore, little is known about the regulation of IGF synthesis or the identity of molecular mediators of IGF actions on the placenta and mother. Thus, future research could aim to antagonise IGFs actions and/or their specific receptors and determine the effect/s on pregnancy and postnatal outcomes, so that perhaps IGF-I or IGF-II may be targeted specifically to the placenta and/or particular maternal tissues. Moreover, researchers could explore therapeutic options of increasing endogenous IGF synthesis, perhaps by nutritional means. Since maternal IGF treatment is likely to be most efficacious in early gestation, before the onset of impaired fetal growth, an additional focus should be developing better methods for identifying pregnancies at risk of intrauterine growth restriction.

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